Trial protocol

Intensity-modulated radiotherapy (IMRT) combined with toripalimab in unresectable local recurrent nasopharyngeal carcinoma: a single-center and single-arm phase II clinical trial

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1. Abstract

Local recurrence is one of the most challenging issues to arise in the treatment of nasopharyngeal carcinoma, and approximately 10 to 15% of primary nasopharyngeal carcinoma patients will experience local recurrence. Minor recurrent lesions can be treated with salvage surgery, but most lesions still cannot be surgically removed.

The main treatment for unresectable locally recurrent nasopharyngeal carcinoma (rNPC) is still secondary-course radiotherapy. According to the 2018. V2 NCCN guidelines, intensity-modulated radiotherapy (IMRT) is the main treatment for rNPC. However, the efficacy remains poor, even if intensity-modulated radiotherapy (IMRT) is used. The 5-year overall survival rate of rNPC treated with repeated IMRT is approximately 13.2-36%, and there are also limited benefits from combined chemotherapy or molecular-targeted therapy. Thus, there is an urgent need to improve treatment options and their efficacy for patients with unresectable rNPC.

Immunotherapy has emerged as a promising treatment approach in recent years. Immunotherapy has fewer adverse reactions and longer-lasting action than chemotherapy and molecular targeted therapy, which could potentially improve the survival outcomes and quality of life of patients. At present, numerous studies both at home and abroad have shown that PD-1 monoclonal antibodies could significantly prolong the survival time of patients with various cancers, such as malignant melanoma and lung carcinoma. Regarding the research on the application of PD-1 monoclonal antibodies in nasopharyngeal

carcinoma, a number of clinical studies have been carried out in our hospital, among which an open-label phase II clinical trial by Prof. Ruihua Xu's team initially found that the objective response rate (ORR) of patients with recurrent and metastatic nasopharyngeal carcinoma treated with toripalimab was 30.8%, and the disease control rate (DCR) was 61.5%, which is an inspiring result (https://oncologypro. esmo.org/Meeting-Resources/ESMO-2018-Congress).

Toripalimab is a humanized anti-programmed cell death-1 (PD-1) IgG4K (γ4,κ) monoclonal antibody (mAb) that is a coinhibitory receptor expressed on T cells. By binding to PD-1, it sterically blocks the binding of PD-1 and PD-L1/PD-L2, increasing the activity of T lymphocytes; it can also lower the expression on the cell membrane surface of PD-1 by inducing the endocytosis of PD-1, thereby enhancing the ability of T lymphocytes to react to antigen stimulation and exert antitumor effects. In this study, we intend to carry out a single-arm clinical trial using IMRT combined with toripalimab to treat unresectable rNPC in order to clarify the efficacy and safety of this new combination therapy. Confirmation that IMRT combined with toripalimab is safe and effective for the treatment of rNPC will provide the evidence needed for an expanded phase III clinical trial to improve the therapeutic effect of IMRT plus PD-1 therapy in rNPC patients.

2. Project basis

Nasopharyngeal carcinoma is one of the most common malignant carcinomas in China, with the highest incidence being in South China and

Hong Kong. According to the data released by the National Cancer Center in 2018, the number of new cases of nasopharyngeal carcinoma in China in 2014 was estimated to be 44,600, with 24,200 attributable deaths, and its incidence ranks 20th among malignant carcinomas. Nasopharyngeal carcinoma usually occurs during prime adulthood, and it is likely to cause major impacts on society, economy, labor, and families. Radiotherapy combined with or without chemotherapy is the primary initial treatment of nasopharyngeal carcinoma. Due to advancements in radiotherapy technology, the 5-year overall survival rate for the initial treatment of nasopharyngeal carcinoma is approximately 80% [1-5]. However, 10-15% of patients will have local recurrence [3, 6-8].

Our previous research found that approximately 38% of locally recurrent carcinomas (rT1-2N0M0) can be treated with salvage surgery, and the operable scope includes rT1N0M0, rT2N0M0 (carcinoma confined to the surface of the parapharyngeal space), rT3N0M0 (carcinoma confined to the bottom of the sphenoidal sinus), and rT0N1-3M0 (carcinoma does not infiltrate the cervical spine, brachial plexus, neck muscles, carotid artery), but most of the lesions (62%) still cannot be surgically removed [9]. For inoperable locally recurrent nasopharyngeal carcinoma, although two-course radiotherapy, palliative chemotherapy or combination therapy have proven to be effective treatments for patients with locally recurrent nasopharyngeal carcinoma, based on our research, we have found that second-course radiotherapy is still the most effective and widely applicable treatment method among the various options available for inoperable recurrent nasopharyngeal carcinoma. Due to the development of radiotherapy technology, radiotherapy technologies such as two-dimensional radiotherapy, three-dimensional conformal radiotherapy, post-loading radiotherapy, stereotactic radiotherapy, and intensity-modulated radiotherapy have been incorporated into clinical practice [10-13]. However, our previous research found that intensity-modulated radiotherapy (IMRT) can significantly prolong the survival time of nasopharyngeal carcinoma patients compared with traditional two-dimensional radiotherapy [14], and due to the accuracy of the radiation dose and the protection offered to surrounding normal tissues, intensity-modulated radiotherapy (IMRT) has been recommended as the preferred radiotherapy technique for nasopharyngeal carcinoma treatment by the NCCN treatment guidelines [14-16]. Even so, current domestic and foreign reports show that the effect of IMRT in recurrent NPC is still poor, with a 5-year OS rate of only 13.2-36%[16-21]. According to the 2018 V2 NCCN guidelines, radiotherapy is the first choice for the treatment of inoperable and locally recurrent nasopharyngeal carcinoma.

This study is a single-arm, open phase II clinical trial using Simon's two-phase optimal design. The main purpose of the study is to evaluate the effectiveness and safety of intensity-modulated radiotherapy combined with toripalimab for the treatment of locally recurrent inoperable nasopharyngeal carcinoma. Previous retrospective studies have shown that the response rate after radiotherapy for nasopharyngeal carcinoma has a striking correlation with overall survival (OS), failure-free survival (FFS) and distant metastasis-free survival (DMFS). Multivariate analyses have also shown that the response rate is an independent prognostic indicator of OS, FFS, and DMFS [22-24]. Therefore, this study proposes an objective response rate (ORR) of 50% for unresectable nasopharyngeal carcinoma [25] as the reference value for sample size estimation in this study.

Synchronous radiochemotherapy is the standard treatment for advanced nasopharyngeal carcinoma. However, the 5-year OS rate in recurrent locally advanced nasopharyngeal carcinoma is only 34.3% [21], and the toxicity and side reactions are severe, with grade 3-4 toxicities and side reactions occurring in up to 53% of patients [26], indicating poor tolerance. For molecular targeted drug therapy, phase II clinical trials have proven that targeted drugs have limited therapeutic effects in recurrent nasopharyngeal carcinoma, with 2nd- and 3rd-line treatment failure being observed and an efficacy rate of only

11.7%; moreover, drug resistance is inevitable, which limits further improvements in efficacy [27]. Therefore, there is an urgent need for a new method to replace conventional chemotherapy with a treatment option that can assist intensity-modulated radiotherapy and improve the treatment effect in patients with locally recurrent nasopharyngeal carcinoma.

Immunotherapy is an emerging carcinoma treatment method in recent years. Compared with chemotherapy and molecular targeted therapy, immunotherapy has mild adverse reactions and long-lasting effects. Among them, PD-1, an immune checkpoint inhibitor, is an inhibitory molecule of T cells. Its binding with the ligand PD-L1 plays an immunosuppressive role and is an important mechanism for cancer immune escape [28]. Immunotherapy based on blocking the PD-1 and PD-L1 pathways has attracted much attention. Preliminary clinical studies have found that for melanoma, the objective response rate of PD-1 monoclonal antibodies in initial and advanced treatment can reach 37%, with a median overall survival time of 32.3 months [29], which has become a hot topic for researchers. In recent years, because the curative effect of PD-1 antibodies is distinct, the FDA has approved a variety of PD-1 and PD-L1 monoclonal antibodies used in the treatment of melanoma, advanced non-small-cell lung carcinoma, renal cell carcinoma, etc. At the same time, a number of clinical trials of PD-1 and PD-L1 monoclonal antibodies alone or combined with traditional radiotherapy and chemotherapy are in progress; however, the efficacy of PD-1 monoclonal antibodies combined with radiotherapy in recurrent nasopharyngeal carcinoma has not yet been reported.

Studies have confirmed that radiotherapy not only has a direct killing effect on cancer cells but also triggers an immune-mediated anticancer response, especially when combined with immunotherapy [30]. However, it can also cause some damage to immune cells at exposed sites. Therefore, radiotherapy is usually considered to suppress the immune effect of the body.

Recent studies have found that radiotherapy can also activate the anti-carcinoma immune response [31-34]. For example, radiotherapy can release large amounts of cancer-associated antigens by killing cancer cells and cancer stromal cells; at the same time, radiotherapy can promote the immune response by enhancing antigen presentation [32, 34]. Radiotherapy can induce T cell responses, significantly increase the proliferation and activation level of T cells in the cancer lymphatic drainage area, and enhance the anti-carcinoma immune response mediated by CD8+ T cells [33]. In addition, the increase in cancer infiltrating lymphocytes after radiotherapy also proves the activation effect of radiotherapy on the immune system [31]. At present, clinical studies have confirmed that in the treatment of advanced melanoma, the CR rate of PD-1 monoclonal antibody combined with radiotherapy is increased by 19.2% compared with that of PD-1 monotherapy, and the median survival time (MST) is extended by 9 months [35]. Therefore, the above theoretical bases and clinical practice show that the combined application of radiotherapy and immunotherapy is feasible and effective.

In the current clinical trials of immunotherapy combined with radiotherapy, different clinical trials place immunotherapy before, after or at the same time as radiotherapy. However, existing studies have shown that carcinomas can release and expose new antigens after local radiotherapy, which can change the tumor microenvironment and systemic immune response [31-34]. Therefore, using radiotherapy to release new carcinoma antigens and combining immunotherapy can achieve better therapeutic effects. At present, clinical studies have shown that radiotherapy has a positive effect on the immune system [36, 37]; clinical studies have confirmed that for the treatment of advanced melanoma, the CR rate is increased by 19.2%, and the median survival time is extended by 9 months with combination treatment compared to treatment with PD-1 inhibitor alone [34]. For malignant gliomas, the combination of stereotactic radiotherapy and checkpoint inhibitors also improved overall survival by 15% [38]. For adjuvant immunotherapy after radiotherapy, the PACIFIC trial proved that, in locally advanced non-small-cell lung carcinomas (NSCLCs) that have not progressed after concomitant radiochemotherapy with platinum-based regimens, administration of PD-1 monoclonal antibody after radiotherapy can prolong the PFS of patients to 16.8 months, and the PFS of the placebo group was only 5.6 months. The experimental group had a 2-year overall survival rate that was 10.7% higher than that of the placebo group [39, 40]. These studies provide valuable evidence for the timing of combined radiotherapy with PD-1/PD-L1 monoclonal antibodies. Considering the fatal and subfatal injuries induced by radiotherapy, apoptotic carcinoma cells will continuously release cancer antigens; therefore, combined immunotherapy during and after radiotherapy may be the most appropriate combination.

Regarding the application of PD-1/PD-L1 inhibitors in nasopharyngeal c arcinoma, our hospital has carried out a number of clinical studies and o btained inspiring results. Two clinical trials by Prof. Zhang Li explored th e safety and efficacy of camrelizumab and combined therapy of camreliz umab+gemcitabine+cisplatinum in advanced or recurrent NPC. In advance d or recurrent NPC, the response rate of camrelizumab as a single drug is 34%, the severe adverse reaction rate is only 16%, and the respons e rate of combined therapy is as high as 91%. Camrelizumab and combi ned therapy show good safety and significant efficacy in NPC [41]. An o pen phase II clinical study conducted by Professor Ruihua Xu's team fou nd that the objective response rate (ORR) and disease control rate (DC R) of patients with recurrent and metastatic nasopharyngeal carcinoma tr eated with toripalimab reached 30.8% and 61.5%, respectively (https://on cologypro.esmo.org/Meeting-Resources/ESMO-2018-Congress/Recombinant -Humanized-Anti-PD-1-Monoclonal-Antibody-JS001-in-patients-with-refractory -metastatic-nasopharyngeal-carcinoma-PreliminarY-results-of-an open-label-t he phase-II-a clinical study). These studies provide a feasibility basis for the application of PD-1/PD-L1 inhibitors in nasopharyngeal carcinoma. Ho wever, how to combine immunotherapy for recurrent nasopharyngeal carc inoma is still unknown.

Toripalimab is a humanized anti-human programmed cell death-1 (PD-1) IgG4K (γ4,κ) monoclonal antibody (mAb) that is a coinhibitory receptor expressed on T cells. Toripalimab introduces a serine to proline 228 and minimizes replacement of the Fab chain. Similar to other anti-PD-1 antibodies, it has a high affinity and blocks the binding of PD-1 and its ligand (programmed cell death ligand 1 (PD-L1;B7-h1 or CD274)). However, it differs from other ligands in that it binds to PD-1 for a longer period of time (measured by the dissociation constant).

In this study, we intend to use IMRT combined with toripalimab in the treatment of unresectable locally recurrent nasopharyngeal carcinoma through a single-arm clinical trial to clarify the safety and efficacy of this new treatment. Once IMRT combined with toripalimab can be proven to be safe and effective for the treatment of locally recurrent nasopharyngeal carcinoma, it will be able to fill the need for radiotherapy combined with immunotherapy in nasopharyngeal carcinoma, provide evidence-based medical evidence to support an expanded phase III clinical trial, and improve the treatment efficacy of patients with unresectable locally recurrent nasopharyngeal carcinoma.

3. References

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4. Research content

1. Ethical considerations

Advantages and disadvantages of toripalimab combined with intensity modulation radiation therapy (IMRT) for the treatment of unresectable local recurrent nasopharyngeal carcinoma:

1) Advantages:

a) Toripalimab combined with intensity-modulated therapy can fully mobilize the patient's autoimmunity, which is expected to improve the local control rate and the overall survival of the patient.

b) IMRT can enhance the efficacy of immunotherapy by killing cancer cells and releasing tumor antigens.

2) Disadvantages:

a) The price of toripalimab would increase the financial burden of patients;

b) Toripalimab combined with intensity-modulated therapy may cause more adverse reactions than radiotherapy alone.

Although the use of toripalimab increases the economic burden and toxicity reactions in the early stage of treatment to a certain extent, the local control and overall survival rates are expected to improve after combined immunotherapy. Therefore, based on comprehensive consideration, for patients with inoperable local recurrent nasopharyngeal carcinoma, the advantages of toripalimab combined with modulation therapy outweigh the disadvantages.

2. Sample size estimation

Simon's two-stage optimal design is adopted in this trial. The main objective of this study is to investigate the objective response rate (PR+CR) of PD-1 combined with radiotherapy for the treatment of unresectable rNPC. According to previous studies, if the effective rate of PD-1 combined with radiotherapy is ≤50%, it is considered invalid. The effective rate of PD-1 combined with radiotherapy is expected to be ≥75%, α=0.05, β=0.2, and the optimal two-stage design is 6/11 (16/25). In the first stage, 11 patients will be enrolled. If the number of patients with objective response (CR+PR) is ≤6, the trial will be terminated. Otherwise, 14 patients will be enrolled in the second stage; i.e., a total of 25 patients will be enrolled. If the number of patients with an objective response (CR+PR) exceeds 16 among all patients in the two stages, the combination of PD-1 and IMRT will be considered a success.

3. Estimated time for case collection

The enrollment of 25 patients will be completed at Sun Yat-sen University Cancer Canter, and the eligible patients will account for approximately 5-10% of the total recurrent nasopharyngeal carcinoma in the hospital annually. It is estimated that 50% of the eligible patients refuse to enter the trial; thus, 25 cases will be collected within half a year.

4. Grouping method

This clinical trial employs an open-label single-arm design.

5. Screening period inspection

During the screening period of this study, the following laboratory examination samples will be sent to the laboratory of our center for analysis.

5.1 Examinations to be completed within 2 weeks before treatment

1) Personal data.

2) Physical examination, including height, weight and vital signs.

3) Nasopharyngoscopy and physical examination of the head and neck, including cervical lymph nodes.

4) Thoracoabdominal and general physical examination.

5) Routine blood, urine, and biochemical marker panels, assessment of blood coagulation function and thyroid function, evaluation of HBV serology, HCV serology, HIV testing, and EB virus serology, in blood samples.

5.2 Examinations to be completed within 1 month before treatment

1) Electrocardiogram.

2) Enhanced MRI of the nasopharynx + neck (enhanced CT is used instead for patients who are unable to undergo MRI examination).

3) PET/CT examination.

5) Histopathological examination of biopsies.

6) Confirmation of eligibility and signing of informed consent.

5.3 Tumor tissue specimens

Samples of tumor tissue (archived or freshly collected) before treatment will be obtained before enrollment, and a pathological report will be completed.

Paraffin-embedded (preferred) or fresh nasopharyngeal malignant tumor specimens will be used for exploratory biomarker analysis (including immune-related or NPC biologically related markers, such as PD-L1 expression, genomic characteristics including tumor mutation burden, neoantigen burden, copy number burden, etc.).

5.4 Selection of subjects

5.4.1 Inclusion criteria

1) A recurrence time of more than 12 months from the end of the initial radiotherapy.

2) Histological and/or cytological diagnosis of recurrent nasopharyngeal carcinoma (differentiated or undifferentiated type, WHO classification type II or III).

3) Radiotherapy site having at least one measurable lesion by MRI examination (according to the RECIST v1.1 standard).

4) Clinical stage: rT0-4N1-3M0 or rT2-4N0M0, stage II-IVA (AJCC 8th edition).

5) Age: 18-65 years old.

6) ECOG status of 0 or 1.

7) Good organ function as defined by the following:

① Hematology: Leukocytes ≥ 4000/μL, neutrophils ≥ 2.000/μL, hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/μL;

②Liver function: Bilirubin ≤ 1.5 times the upper limit of normal (ULN) (patients with Gilbert's disease and a serum bilirubin level ≤ 3 times the ULN may be enrolled), AST and ALT ≤ 3 times, and alkaline phosphatase ≤ 3 times the ULN; albumin ≥ 3 g/dL;

③ International normalized ratio (INR), prothrombin time (PT) or activated partial thromboplastin time (aPTT) ≤ 1.5 times; and

④ Renal function: Serum creatinine ≤ 1.5 times ULN or creatinine clearance ≥ 60 mL/min according to the Cockcroft-Gault formula.

8) Expected survival ≥3 months.

9) Agree to sign an informed consent form and willing to comply with the scheduled visits, treatment plan, laboratory tests and other study procedures.

10) Fertile women will be required have a negative urine or serum pregnancy test within 7 days of enrollment and agree to conduct effective contraception during the study period and at least 60 days after the last administration, including chemotherapy and toripalimab.

11) Male subjects who have a female partner who is still fertile will be required to agree to use effective contraception during the study period and for at least 120 days after the last administration.

5.4.2 Exclusion criteria

1) Resectable recurrent nasopharyngeal carcinoma:

a. rT1N0M0

b. rT2N0M0 (confined to the surface of the parapharyngeal space and more than 0.5 cm away from the internal carotid artery)

c. rT3N0M0 (confined to the wall of the sphenoid sinus and more than 0.5 cm away from the internal carotid artery and the cavernous sinus)

d. rT0N1-3M0 (without invasion into the cervical spine, brachial plexus, neck muscles, carotid artery)

2) A history of severe hypersensitivity to any component of other monoclonal antibodies or PD-1 monoclonal antibodies.

3) Patients with other malignant tumors.

4) Patients with a known or suspected autoimmune disease, including dementia and seizures.

5) Co-occurring serious mental illness.

6) Patients with nasopharyngeal necrosis, radiation-induced brain injury,

severe neck fibrosis, etc., who are not suitable for radiotherapy assessed by the PI.

7) Severe heart disease, lung dysfunction, heart function, or lung function lower than grade 3 (including grade 3).

8) The laboratory test values within 7 days before enrollment do not meet relevant standards.

9) Received systemic or local glucocorticoid therapy within 4 weeks before enrollment.

10) Complications requiring long-term use of immunosuppressive drugs.

11) Patients with active tuberculosis (TB) who are receiving anti-TB treatment or who have received anti-TB treatment within 1 year prior to screening.

12) Patients who use traditional antitumor herbs within 4 weeks before enrollment.

13) Prior use of anti-PD-1/PD-L1 antibodies or anti-CTLA-4 antibodies (or any other antibodies acting on T-cell co-stimulation or checkpoint pathways) and anti-angiogenic agents.

14) Subjects with any active autoimmune disease or a history of autoimmune disease (including interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, nephritis, hyperthyroidism, and hypothyroidism; patients with vitiligo and patients who achieved complete remission of asthma in childhood and needed no intervention after adulthood were enrolled, but patients with asthma requiring medical intervention with bronchodilators were not included).

15) HIV positivity.

16) HBsAg positivity and HBV DNA copy number positivity (quantitative detection ≥ 1000 cps/ml); chronic hepatitis C with blood screening positivity (HCV antibody positive).

17) The receipt of any anti-infection vaccines (such as influenza vaccine, varicella vaccine, etc.) within 4 weeks before enrollment.

18) Pregnant women of childbearing age and lactating women.

6. Protocol, Course of Treatment and Dose

6.1 Treatment plan

Total radiotherapy dose: PTVnx 60 Gy/27 F, PTVnd 60 Gy/27 F, PTV1 54 Gy/27 F, once a day, 5 days a week.

Toripalimab administration with the first day of radiotherapy: 240 mg, intravenous injection for more than 60 minutes, Q3W, lasting until 3 months after the end of radiotherapy (maximum of 7 cycles).

Criteria of Treatment Termination

1. Intolerable toxicity;
2. Occurrence of disease progression (according to RECIST criteria);
3. Any concomitant treatments during the trial have a significant impact on the safety and efficacy of the experimental drugs;
4. Pregnancy during the study period;
5. Other conditions for which continued administration is not considered appropriate by the investigator.

6.2 Criteria of Radiotherapy Suspension

1) Hematologic examination of the patients revealing leukocytes < 2×109/L or absolute values of neutrophils < 1.0×109/L and platelets < 50×109/L.

2) Severe gastrointestinal reactions caused by radiotherapy, such as anorexia, nausea and vomiting, that do not improve after general clinical treatment.

3) Increase in body temperature to 38.5°C.

4) Severe acute radiotherapy reactions such as severe throat erosion or oral ulcers.

6.3 Criteria for withdrawal from the test

5) Severe treatment complications:

A) Grade IV neutropenia

B) Grade IV acute mucositis

6) The desire to withdraw from the study at any time

7) Disease progression during treatment

8) Other diseases that occur during treatment that significantly affect the general condition of the patient and lead to the treatment to be stopped.

6.4 Design and dose of radiotherapy plan:

Table 1 IMRT and important organ delineation principles for nasopharyngeal carcinoma.

Name	Definition	Remarks
GTVnx	All gross nasopharyngeal lesions confirmed by clinical and imaging examinations.	Primary nasopharyngeal lesion
GTVnd	Positive lymph nodes touchable or visible on imaging examinations (Imaging diagnostic criteria: ① Short diameter of the largest cross-section ≥1 cm; ② Necrotic foci in the center; ③ Extracapsular invasion; ④Short diameter of clusters ≥0.8 cm; ⑤ PET-CT showing positive lymph nodes).	Metastatic cervical lymph nodes
CTV	Encompass the GTVnx with a radial margin of 0.5-1 cm; expansion distance can be determined according to the characteristics of the adjacent tissue structure.	High-risk micro-infiltration area
PTV	PTVnx, PTVnd, and PTV1 are the external expansion of GTVnx, GTVnd, and CTV by a certain distance, generally 0.3 cm in the forward, up, down, left, and right directions, and 0.1~0.3 cm in the backward direction.	

Organ at risk	Brain stem, temporal lobe, lens, eyeball, optic nerve, optic chiasm, pituitary gland, parotid gland, temporomandibular joint, mandible, larynx, oral cavity, submandibular gland, inner ear, middle ear.	Items can be increased or decreased as appropriate according to the tumor situation

Table 2. Normal tissue dose constraints used for plan optimization

Structure	Dose constraints
Brain stem_ PRV	D1* ≤ 64 Gy
Spinal cord_PRV	D1^ ≤ 50 Gy
Optic nerves_PRV	D1* ≤ 60 Gy
Optic chiam_PRV	D1* ≤ 60 Gy
Temporal lobe	D1* ≤ 64 Gy
Inner ear	Dmean# ≤ 50 Gy
Pituitary	D1* ≤ 60 Gy
Mandible	D1^ ≤ 70 Gy
Temporomandibular Joint	D1^ ≤ 70 Gy
Parotid	Dmean ≤ 26 Gy
Larynx	Dmean ≤ 45 Gy
Oral cavity	Dmean ≤ 45 Gy

The following table describes the normal tissue dose constraints for reirradiation to the patients whose tumor recurrence occurs more than 3 years after initial radiotherapy; if the recurrence occurred within 3 years after initial radiotherapy, the normal tissue dose constraints for reirradiation should be 2/3 of the following table describes.

PRV = planning organ at risk volume.

* Dose received by 1% of the target volume

^ Dose received by 1 cc of the target volume.

7. Additional treatment

Patients with tumor progression after treatment may receive salvage treatment, including salvage surgery and chemotherapy as appropriate, but no third course of radiotherapy.

8. Observation and evaluation of the trial

8.1 Initial Screening Period

As all patients are under standardized management for NPC, they need to undergo a series of examinations as well as provide relevant information to confirm their pathologic diagnosis and clinical stage before being admitted to the trial, including the following:

1) Medical history review

2) Personal data collection

3) Review of present medications and treatment

4) Body examinations, including height, weight, and vital signs

5) Physical examination of the head and neck region, including the nasopharyngeal and cervical LNs

6) Physical examination of the nervous system

7) Nasal endoscopy and lesion biopsy

8) Biopsy

9) Routine blood panel

10) Urine routine

11) Blood biochemistry

12) Thyroid function test

13) Myocardial enzyme assay

14) Adrenal gland and pituitary hormone test

15) Imaging test of the tumor (enhanced MR or enhanced CT of the head and neck (CT was indicated only in patients with contraindications to MRI))

16) PET/CT is compulsorily required during the initial screening period*

*Patients who underwent PET/CT examinations do not need chest X-rays, abdominal ultrasonography, or ECT bone scans.

8.2 During Treatment

The following aspects need to be assessed from the start to the end of treatment.

a. MRI and/or CT of the primary tumor, which will be performed after treatment, and CR, PR, SD, or PD will be evaluated according to the RECIST version 1.1 criteria. Chest films and abdominal ultrasonography will be reexamined after treatment. PET-CT and ECT bone scans will be performed as clinically indicated. We define complete response (CR) as a complete lack of unequivocal soft tissue mass in the local region and cervical lymph nodes that all had a short axis of less than 10 mm according to the RECIST guidelines. Imaging results to assess the ORR and progression-free survival are centrally reviewed.

b. General conditions

c. Acute and late toxicity assessment (NCI-CTC, version 5.0), including hematological toxicity, gastrointestinal reactions, hepatotoxicity, nephrotoxicity, mucositis, neurotoxicity, ototoxicity, thyroid function, myocardial enzymes, adrenal glands and pituitary hormones.

d. Peripheral neuropathy

e. Laboratory tests: Routine blood tests and blood biochemistry are required within 1 week prior to each cycle of immunotherapy and once per week during treatment. Thyroid function, myocardial enzymes, the adrenal gland and pituitary hormones are required once per 2 cycles of immunotherapy.

8.3 Follow-Up and Recording of Events

After completing radiotherapy, the patients are followed up every 3 months until disease progression or death to evaluate the patients' recent and long-term efficacy and safety profiles.

Follow-up method: Record of the patient's examination data, a doctor's letter with signature to document the visit, or a doctor's follow-up records collected by telephone.

Follow-up content: Routine examination of the nasopharyngeal lesions and LNs every 3 months and abdominal B-mode ultrasound and chest X-ray every 6 months. PET/CT or bone scintigraphy are performed when clinically indicated. The treatment responses were also evaluated according to the RECIST criteria. The earliest date of detecting symptomatic late toxicities and the eventual maximum grade according to the Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) are recorded.

9 Risks Associated with Toripalimab

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapies may increase the risk of immune-mediated adverse events, particularly the induction or exacerbation of autoimmune diseases. Potential immune-mediated adverse events, including interstitial lung disease, hypothyroidism and hyperthyroidism, liver dysfunction, pancreatitis, hyperglycemia and adrenal insufficiency, have been observed in clinical studies of the safety and efficacy of toripalimab injection (JS001) in the treatment of solid tumors. For more information on clinical safety, see the Tripletrumab Injection (JS001) Investigator's Manual.

10 Overall plan for managing security issues

10.1 Monitoring

In this study, safety will be assessed by monitoring all serious and nonserious adverse events (adverse events will be defined and graded according to NCI CTCAE version 5.0 criteria). Laboratory values must be reviewed before each infusion.

General safety assessments include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood cell counts.

Patients will be closely monitored for signs and symptoms of autoimmune diseases and infections during the study.

After the final administration of the study drug, patients will be followed for a safety period of 60 days.

After completion of the study or withdrawal from the study, patients who still have an adverse event associated with the study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer therapy is initiated, the patient is lost to follow-up, or the patient withdraws consent, or it has been determined that study treatment or participation in the study does not result in an adverse event.

10.2 Management of toxicity associated with or possibly related to toripalimab should be in accordance with standard medical practice. Other tests, such as autoimmune serologic tests or tissue biopsies, should be used to determine the possible immunogenic cause.

Although most immune-mediated adverse events observed after immunomodulator use are mild and self-limiting, they should be detected early and treated promptly to avoid potentially serious complications. Discontinuation of toripalimab may not produce a direct therapeutic effect, and in severe cases, immune-mediated toxicities may require urgent treatment with topical corticosteroids, systemic corticosteroids, mycophenolate mofetil, or TNF-α inhibitors.

Prior to subsequent administration of toripalimab, researchers should consider the benefit-risk balance for each patient. Toripalimab should be discontinued permanently in patients with life-threatening immune-mediated adverse events.

The most common irAEs included fatigue, pruritus, diarrhea, decreased appetite, rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation, and nausea.

Checkpoint inhibitors should be discontinued in patients with grade 2 (moderate) immune-mediated toxicities and should not be restarted until symptoms or toxicities resolve to grade 1 or less. If symptoms do not resolve within one week, treatment with corticosteroids (prednisone ≤ 10 mg/day or equivalent) should be used.

Patients who develop grade 3 or 4 (severe or life-threatening) immune-mediated toxicities should be permanently discontinued from checkpoint inhibitor therapy. Large doses of corticosteroids (prednisone 1-2 mg/kg/day or equivalent) should be administered. When symptoms resolve to grade 1 or less, the steroid dose may be tapered over at least 1 month.

Infliximab (5 mg/kg) may be administered if symptoms do not improve significantly after 3 days of intravenous steroid administration.

11. Security Measures and Quality Control

1) Provide a systemic learning program for every member in the research group.

2) Make a monitoring plan for adverse effects and an emergency plan.

3) Research plan is approved by the ethics committee.

4) Develop various standard operation procedures related to this study

5) Establish a standardized evaluation system to unify the diagnostic criteria, curative effect judging criteria, etc.

6) Establish professional statistical plans

7) Arrange a quality controller to create a quality control plan and regularly check on the study

8) Set up a coordination committee, curative effect judging group and follow-up team

11. Research endpoint

11.1 Primary endpoint: overall response rate (ORR)

The objective response rate (ORR) is defined as the proportion of patients whose tumor shrinks to achieve a complete or partial response and remains for a certain time. Clinical and imaging examinations are performed to observe and record the regression of nasopharyngeal and neck lesions. The evaluation indicators were complete response (CR), partial response (PR), stable disease

(SD), or progressive disease (PD), and the tumor response rate is calculated. We defined a complete response (CR) as a complete lack of unequivocal soft tissue mass in the local region and cervical lymph nodes that all had a short axis of less than 10 mm according to the RECIST guidelines.

11.2 Secondary Study Endpoints

1) Progression-free survival (PFS) is defined as the time from enrollment to the date of tumor progression or death for any reason or the last follow-up if there is no tumor progression.

2) Overall survival (OS) is defined as the time from enrollment to death from any cause or the last follow-up if there is no death.

3) Safety indicators are evaluated by NCI-CTC5.0 standards. Acute toxicity is defined as hematological toxicity, mucositis, allergic reactions, neurotoxicity, gastrointestinal reactions, or other adverse events and serious adverse events.

11.3 Data management

All data from the registered patients meeting the enrollment criteria are sent to the center for management. All databases are managed by specially assigned persons. The data platform will remain available for double input and verification.

11.4 Case report form

A case report form should be designed before the start of the study. The form should be able to record the disease and treatment follow-up comprehensively to facilitate filling and entry into the computer database.

11.5 Statistical analysis

All patients enrolled are included in the efficacy and safety analyses. For all patients, the median follow-up time is calculated using the reverse Kaplan-Meier method. The ORR and 95% CIs are calculated using the Clopper-Pearson method. The duration of response, PFS, and OS are analyzed using the Kaplan-Meier method.

The associations between PD-L1 expression, genome/clinical characteristics and objective response, complete response and PFS are assessed via post hoc analyses. For the comparison between subgroups, $\chi 2$ test or Fisher's exact test and Wilcoxon rank sum test are used to determine complete response. Univariate analysis of the effects of these parameters on PFS is conducted by the Cox proportional hazards model to calculate the hazard ratios and 95% confidence intervals.

12. SCHEMATIC